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HOWARD, ZACHARY C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/977,864	DUDEK ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/26/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,8,9,21 and 23-67* is/are pending in the application.

4a) Of the above claim(s) *4,6,8 and 9* is/are withdrawn from consideration.

5)☒ Claim(s) *32-34 and 44-49* is/are allowed.

6)☒ Claim(s) *1,5,21,25,26,28,30,31,35,36,38,40-43,50-53,56,57 and 60-67* is/are rejected.

7)☒ Claim(s) *23,24,27,29,37,39,54,55,58,59 and 64* is/are objected to.

8)☒ Claim(s) *1,4-6,8,9,21 and 23-67* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/28/08;11/26/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

TAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 11/26/08 has been entered in full. Claims 60, 61, 63 and 64 are amended.

Claims 4, 6, 8 and 9 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim (see below). It is noted that claim 4 depends from claim 1 but recites a genus of cancer ("urogenital") that is broader than any of the species recited in claim 1 (i.e., "prostate" and "bladder" are species of urogenital). It is noted that claim 9 depends from claim 1 but recites a species of unwanted cell proliferation that is not encompassed by claim 1.

Claims 1, 5, 21 and 23-67 are under consideration in the instant application.

Information Disclosure Statement

The IDS of 8/28/08 and 11/26/08 have each been considered.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (8/9/08).

The rejection of claims 60 and 63-67 under 35 U.S.C. § 112, first paragraph at pg 3-5 for failing to provide enablement for the full scope of the claims is *withdrawn* in view of Applicants' amendments to the claims. However, please see the new rejection of these claims under 35 U.S.C. § 112, first paragraph at pg 3-5 for failing to provide enablement for the full scope of the claims, necessitated by Applicants' amendments to the claims.

The rejection of claims 60 and 63-67 under 35 U.S.C § 112, second paragraph, at pg 6 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claims 61-67 under 35 U.S.C. § 112, 1st paragraph at 6-8 is *withdrawn* for containing new matter is withdrawn in view of Applicants' amendments to the claims, and Applicants' persuasive arguments at pg 13-14 of the 11/26/08 response.

The provisional rejection of claims 64-66 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 68 of copending Application No. 10/652,298 is *withdrawn* in view of the amendment to claim 64 that removes the recitation of "overexpresses a *gli-1* gene". Please note that said claims remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 70 of copending Application No. 10/652,298 (see below).

Maintained Objections and/or Rejections

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5, 21, 25, 26, 28, 30, 31, 35, 36, 38, 40-43, 50-53, 56 and 57 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 68 of copending Application No. 10/652,298. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. This rejection was previously set forth

at pg 8-9 of the 8/9/08 Office Action. For clarity, the rejection is reiterated and then Applicants' arguments are addressed.

Each of instant claims 1, 5 and 26 fully encompasses the method of claim 68 of the '298 application, in so far as it is drawn to the species of cancer of the "prostate" or "bladder" tissues. Claim 68 of the '298 application encompasses a method comprising determining whether diseased tissue overexpresses a *gli-1* gene, and contacting an overexpressing tissue with an anti-Sonic hedgehog antibody that inhibits *hedgehog* signaling in order to treat the cancer, wherein the tissue is associated with prostate or bladder cancer. Therefore, claim 68 of '298 anticipates each of claims 1, 5 and 26.

Claims 21, 25, 28, 30 and 31 are of similar scope to instant claim 1, but limit the method to one performed in a patient (i.e., *in vivo*). The specification of the '298 application indicates that *in vivo* treatment is a preferred embodiment of the claimed methods; therefore, claim 68 also anticipates instant claims 21, 25, 28 and 30.

Claims 35, 36 and 38 depend from one of the above claims and limit the parent claim to one wherein the gene measurement is made in a sample obtained from a tumor in a patient. This further limitation is also a preferred embodiment of the '298 application, as evidenced by claim 72 (presented 12/26/07 in the '298 application). Therefore, claim 68 of the '298 application also anticipates claims 35, 36 and 38.

Claims 40-43, 50-53, 56 and 57 each depend from one of the above claims and limit the parent claim to one wherein the *gli-1* overexpression is determined by measuring protein or transcript. These further limitations are also preferred embodiments of the '298 application, as evidenced by claims 76 and 77 (presented 12/26/07). Therefore, claim 68 of the '298 application also anticipates claims 40-43, 50-53, 56 and 57.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In the 11/26/08 response (pg 14), Applicants ask that "this rejection be held in abeyance until indication of allowable subject matter. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter".

The Examiner notes Applicants' intention of submitting a terminal disclaimer; however, the rejection is maintained. See MPEP 804.I.B: "The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications."

Claims 61 and 64-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 70 of copending Application No. 10/652,298. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. This rejection was previously set forth at pg 9-10 of the 8/9/08 Office Action. For clarity, the rejection is reiterated and then Applicants' arguments are addressed.

Each of instant claims 61 and 64-67 fully encompasses the method of claim 70 of the '298 application. Claim 70 of the '298 application encompasses a method comprising determining whether diseased tissue overexpresses a *Sonic hedgehog* gene, and contacting an overexpressing tissue with an anti-Sonic hedgehog antibody that inhibits *hedgehog* signaling in order to treat the cancer, wherein the tissue is associated with prostate or bladder cancer. Instant claims 61 and 64-66 have been amended to recite that the tumor "expresses" (rather than "overexpresses") a *Sonic hedgehog* gene. However, the term "expresses" encompasses the term "overexpresses", as evidenced by instant claim 67, which depends from claim 64 and limits "expresses" to "overexpresses". Therefore, claim 70 of the '298 application anticipates each of instant claims 61 and 64-67.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants' 11/26/08 response does not mention or address this rejection; therefore it is maintained for the reasons of record.

New objections and/or rejections necessitated by Applicants' amendment

Claim Objections

Claim 64 is objected to because of the following informalities:

In line 2 of the claim 64 (as newly amended), in the term "Sonic hedgehog gene", the words "Sonic hedgehog" are not italicized as in line 6 of the same claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for treating colon cancer in a patient in need thereof, comprising determining or ascertaining whether colon cancer tissue overexpresses a *gli-1* or *Sonic hedgehog* gene and administering to said patient in need thereof an amount of a *hedgehog* antibody sufficient to decrease at least one of the growth or proliferation of the colon cancer tissue, wherein the colon cancer tissue overexpresses a *gli-1* gene or *Sonic hedgehog* gene, and wherein the *hedgehog* antibody binds to Sonic hedgehog protein and inhibits *hedgehog* signaling,

does not reasonably provide enablement for:

a method for treating colon cancer, comprising determining or ascertaining whether colon cancer tissue expresses a *gli-1* or *Sonic hedgehog* gene and administering to a patient in need thereof an amount of a *hedgehog* antibody sufficient to decrease at least one of the growth or proliferation of the colon cancer tissue, wherein the colon cancer tissue expresses a *gli-1* gene or *Sonic hedgehog* gene, and wherein the *hedgehog* antibody binds to Sonic hedgehog protein and inhibits *hedgehog* signaling. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

As amended, claims 60-67 differ significantly from the other pending claims by not requiring ascertaining or determining whether colon cancer tissue "overexpresses" a *gli-1* or *Sonic hedgehog* gene and/or not requiring that the treated cancer tissue is cancer tissue that "overexpresses" *gli-1* or *Sonic hedgehog*. In contrast, claim 60-67 only require ascertaining or determining whether colon cancer tissue "expresses" a *gli-1* or *Sonic hedgehog* gene and/or that the treated cancer tissue is cancer tissue that "expresses" *gli-1* or *Sonic hedgehog*. The term "expresses" broadly encompasses "overexpresses", "underexpresses" or no change; i.e., the claims encompass treatment of colon cancer tissue that has overexpression, underexpression or no change in expression of *gli-1* or *Sonic hedgehog* genes as compared to wild type colon tissue.

The relevant art reports a great deal of variation in the reported levels of hedgehog components in colon cancer in primary tumor samples. Chatel et al (2007) teach that "the published results on primary human colon cancers are also confusing. Some authors, but not others detected increased levels of Hh pathway members during colon cancer progression. Moreover, the expression of Ihh and Gli1 were shown to be decreased during colon cancer progression in recent publications" (see pg 2626 of Chatel et al, 2007. Int J Cancer. 121: 2622-2627; cited previously). Douard et al (2006) examined primary tumor samples from 44 patients with colorectal adenocarcinomas and found that 86% (38 of 44 patients) had increased Shh mRNA as compared to normal adjacent tissue (pg 668), and this correlated with increased Gli1 expression (Douard et al, 2006. Surgery. 139: 665-70). However, Bian et al (2007) examined primary tumor

samples from 25 patients with colorectal adenocarcinomas and found that a much lower percentage of the samples overexpressed Shh mRNA or protein as compared to normal tissue (Bian et al, 2007. World J. Gastroenterol 13(11): 1659-1665). Specifically, in only 10 of 25 samples was Shh mRNA detectable by in situ hybridization (confirmed by RT-PCR), and only in 13 of 25 was Shh protein detectable by immunohistochemistry. Yauch et al (2008) teach that "microarray expression analysis of human tissue specimens revealed that subsets of colorectal … cancers overexpressed Hh ligand mRNA (data not shown)" and that RT-PCR "profiling of an independent set of human tissue specimens confirmed that transcript levels of SHH ... ligands were significantly upregulated in subsets of [colorectal] cancers (Fig. 2a-c)" [2a shows colorectal] (pg 406 of Yauch et al. Nature. 455: 406-410; cited as reference DV on the 8/28/08 IDS).

Despite the variability reported in the art, these results provide evidence that significant subset of colon tumors express, but do not overexpress, the components of the Sonic hedgehog signaling pathway (e.g., the *gli-1* and *Sonic hedgehog* genes). In U.S. Pre-Grant Application Publication 2004/0110663 (cited on the 12/13/07 IDS; a publication of application 10/652,298, which is a continuation-in-part of the instant application), Applicants report that the growth of a xenograft of non-hedgehog expressing colon cancer cell line SW480 is not inhibited by 5E1 (Figure 54; ¶ 848 of the '663 publication). While the text of the specification refers to this cell line as "non-hedgehog expressing", Figure 54 itself actually labels the SW480 cells as "low-SHH Expressing", indicating that this tumor line actually has some SHH expression. Furthermore, Chatel et al (2007; cited previously), demonstrates that SW480 cells actually do express some Shh protein (see Figure 3 on page 2624). Thus, the results presented in the '663 publication provide evidence colon tumor cells that do not overexpress Shh are not inhibited by an anti-Shh antibody.

Thus, the evidence of record suggests that anti–hedgehog antibodies will not treat (i.e., inhibit the growth) of colon cancer tissue that is not overexpressing components of the Sonic hedgehog signaling pathway (e.g., the *gli-1* and *Sonic hedgehog* genes). In order to practice the claimed method while excluding those tumors for which *gli-1* or *Sonic hedgehog* gene is not overexpressed, the skilled artisan must

have a means of distinguishing such tumors. Thus, the claims require a step of determination of whether the *gli-1* or *Sonic hedgehog* gene is overexpressed in the tumor. Without such a step, the clinician will be practicing the claimed method "blindly", i.e., without any predictability as to the success of the method.

Due to the large quantity of experimentation necessary to determine how to successfully apply the claimed method to treat a colon tumor that does not overexpress a *gli-1* or *Sonic hedgehog* gene; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to the same; the complex nature of the invention; and the unpredictability of distinguishing colon tumors amenable to anti-hedgehog antibody treatment without measuring *gli-1* or *Sonic hedgehog* gene overexpression, undue experimentation would still be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicants' arguments (11/26/08; pg 11-12) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons. It is noted that Applicants' arguments pertain to the enablement rejection set forth previously and now withdrawn, rather than the new rejection set forth above (necessitated by Applicants' amendments to the claims). However, Applicants' arguments have been fully considered in so far as they apply to the new rejection.

In the response, Applicants argue that in Examples 5 and 8, bladder or colon cancer cells were used to generate a tumor by placing the cells in a mouse host, which was then treated with anti-hedgehog antibody. Applicants argue that these methods "did not include any step of determining gli-1 or Sonic hedgehog gene expression, but treatment with 5E1 still proved effective at reducing the size of the tumor" (pg 11).

Applicants' arguments have been fully considered but are not found persuasive. In Example 5, the bladder cancer was generated from RT-4 cells. As acknowledged by Applicants, Figure 19 shows that the RT-4 cell line expresses *Sonic hedgehog*. However, Figure 19 also clearly shows that the RT-4 cell line overexpresses the *Sonic hedgehog* gene as compared to the control cell line. Thus, prior to conducting the experiment of example 5, the expression of the genes in the tumor tissue had already

been determined or ascertained (presumably, this cell line was selected for the experiment based on the overexpression of *Shh*). In Example 8, the colon cancer was generated from HT-29 cells. The instant specification refers to HT-29 as a "Shh expressing colon cell line", and thus it appears that Applicants had also already determined the level of hedgehog expression, but did not report the specific levels of Shh expression in the specification. However, in U.S. Pre-Grant Application Publication 2004/0110663 (cited on the 12/13/07 IDS; a publication of application 10/652,298, which is a continuation-in-part of the instant application), Applicants report a high level of Shh expression in HT-29 cells (see Figure 36 of the '663 publication, which shows that HT-29 has the highest level of Shh expression of any cancer cell line shown). Thus, in both of these examples, the tumor cell lines that were used overexpressed a component of the hedgehog signaling pathway (the *Sonic hedgehog* gene). The evidence of record (described above) suggests that anti-hedgehog antibodies will not treat (i.e., inhibit the growth) of colon cancer tissue that does not overexpress a component of the Sonic hedgehog signaling pathway (e.g., the *Sonic hedgehog* gene). Furthermore, the relevant art provides evidence that only a subset of colon tumors overexpress components of the hedgehog signaling pathway. In order to practice the claimed method while excluding those tumors for which *gli-1* or *Sonic hedgehog* gene is not overexpressed, the skilled artisan must have a means of distinguishing such tumors. Thus, the claims require a step of determination of whether the *gli-1* or *Sonic hedgehog* gene is overexpressed in the tumor. Without such a step, the clinician will be practicing the claimed method "blindly", i.e., without any predictability as to the success of the method. Working Examples 5 and 8 do not address the non-enabled subject matter because they only concern cancer cell lines that overexpress the *Sonic hedgehog* gene.

Applicants further argue that the skilled artisan would "recognize that information about gli-1 or Sonic hedgehog expression levels could be obtained from a wide variety of sources, and thus a step of determining expression would not be necessary to enable the claimed invention" (pg 11-12).

Applicants' arguments have been fully considered but are not found persuasive. A method step of ascertaining or determining whether a colon cancer tissue expresses

a *gli-1* or *Sonic hedgehog* gene broadly encompasses obtaining such information from a variety of sources. As noted by Applicants, the claims have been amended to include said step. However, for the reasons set forth in the rejection, the claims lack enablement for the full scope of the claimed invention.

Conclusion

Claims 23, 24, 27, 29, 37, 39, 54, 55, 58 and 59 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 32-34 and 44-49 are allowable.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Bridget E Bunner/
Primary Examiner, Art Unit 1647